```
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TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
 NEWS  4  OCT 28   KOREAPAT now available on STN
 NEWS  5  NOV 30   PHAR reloaded with additional data
 NEWS  6  DEC 01   LISA now available on STN
 NEWS  7  DEC 09   12 databases to be removed from STN on December 31, 2004
 NEWS  8  DEC 15   MEDLINE update schedule for December 2004
 NEWS  9  DEC 17   ELCOM reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  10 DEC 17   COMPUAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  11 DEC 17   SOLIDSTATE reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  12 DEC 17   CERAB reloaded; updating to resume; current-awareness
                   alerts (SDIs) affected
 NEWS  13 DEC 17   THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
 NEWS  14 DEC 30   EPFULL: New patent full text database to be available on STN
 NEWS  15 DEC 30   CAPLUS - PATENT COVERAGE EXPANDED
 NEWS  16 JAN 03   No connect-hour charges in EPFULL during January and
                   February 2005
 NEWS  17 FEB 25   CA/CAPLUS - Russian Agency for Patents and Trademarks
                   (ROSPATENT) added to list of core patent offices covered
 NEWS  18 FEB 10   STN Patent Forums to be held in March 2005
 NEWS  19 FEB 16   STN User Update to be held in conjunction with the 229th ACS
                   National Meeting on March 13, 2005
 NEWS  20 FEB 28   PATDPAFULL - New display fields provide for legal status
                   data from INPADOC
 NEWS  21 FEB 28   BABS - Current-awareness alerts (SDIs) available
 NEWS  22 FEB 28   MEDLINE/LMEDLINE reloaded
 NEWS  23 MAR 02   GBFULL: New full-text patent database on STN
 NEWS  24 MAR 03   REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  25 MAR 03   MEDLINE file segment of TOXCENTER reloaded

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.
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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 06:20:39 ON 18 MAR 2005

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 06:20:48 ON 18 MAR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 MAR 2005 HIGHEST RN 845774-58-5
DICTIONARY FILE UPDATES: 16 MAR 2005 HIGHEST RN 845774-58-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
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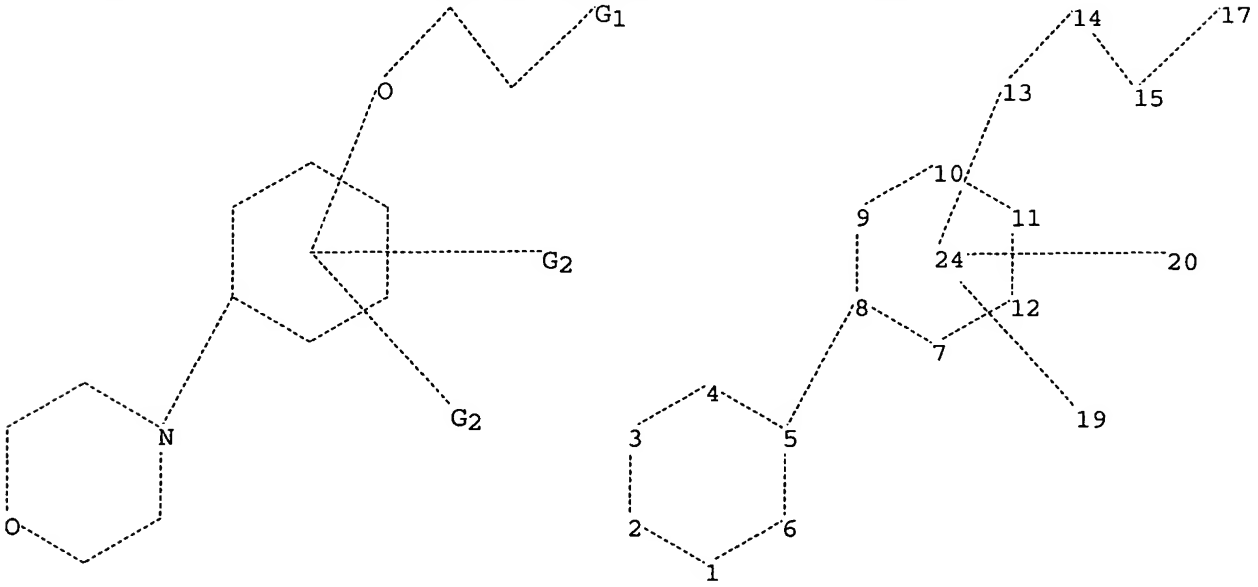


chain nodes :
13 14 15 17 19 20

ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
5-8 13-14 14-15 15-17
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-8 7-8 7-12 8-9 9-10 10-11 11-12 13-14 14-15
15-17
isolated ring systems :
containing 1 : 7 :

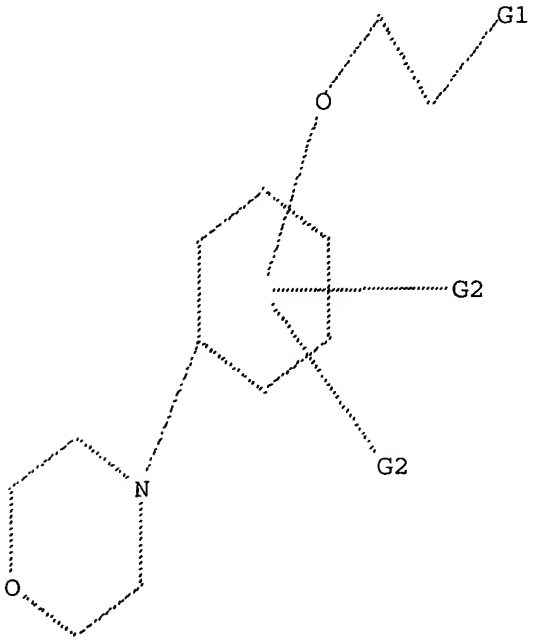
G1:C,O,S

G2:C,H,O

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 C,O,S
G2 C,H,O

Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 06:21:22 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 939 TO ITERATE

```
100.0% PROCESSED     939 ITERATIONS                                  26 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         16942 TO    20618
PROJECTED ANSWERS:              215 TO      825

L2           26 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 06:21:25 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  18870 TO ITERATE

100.0% PROCESSED   18870 ITERATIONS                                520 ANSWERS
SEARCH TIME: 00.00.01

L3           520 SEA SSS FUL L1

=> s l3 and caplus/lc
      45042485 CAPLUS/LC
L4          405 L3 AND CAPLUS/LC

=>
Uploading C:\Program Files\Stnexp\Queries\QUERIES\106746841.str
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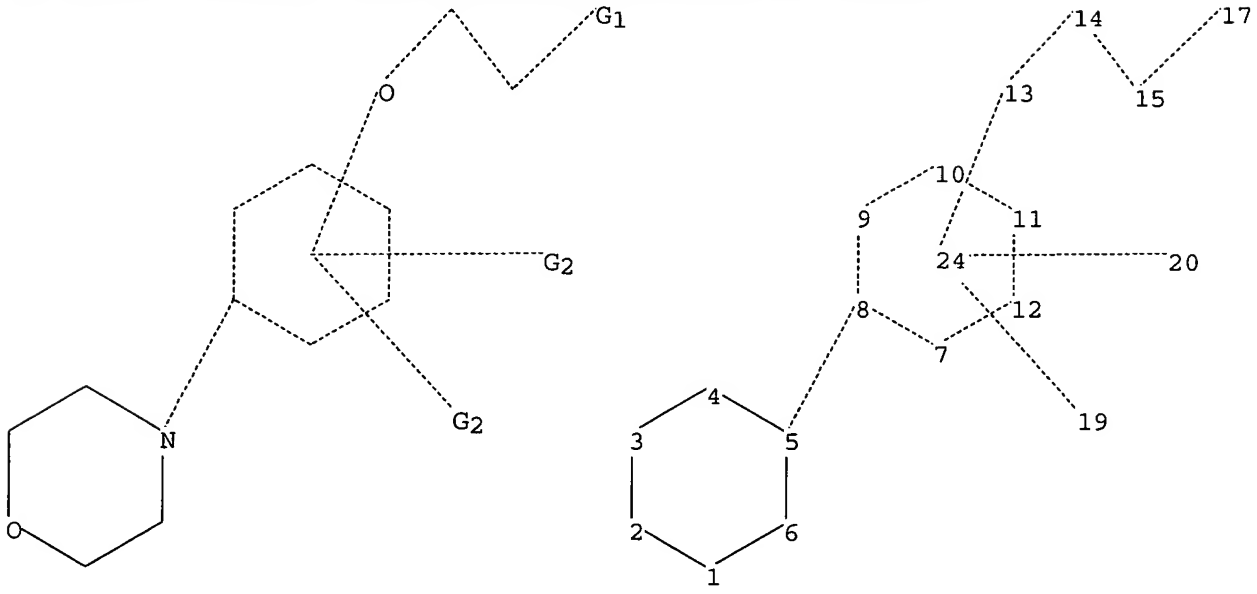



```
chain nodes :
13  14  15  17  19  20
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
5-8  13-14  14-15  15-17
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12
exact/norm bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-8  7-8  7-12  8-9  9-10  10-11  11-12  13-14  14-15
 15-17
isolated ring systems :
containing 1 : 7 :

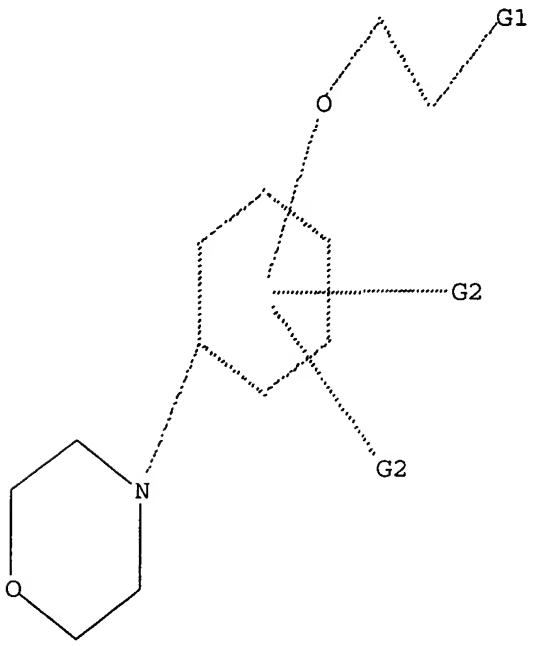

G1:C,O,S
```

G2:C,H,O

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

L5 STRUCTURE UPLOADED

=> d
L5 HAS NO ANSWERS
L5 STR



G1 C,O,S
G2 C,H,O

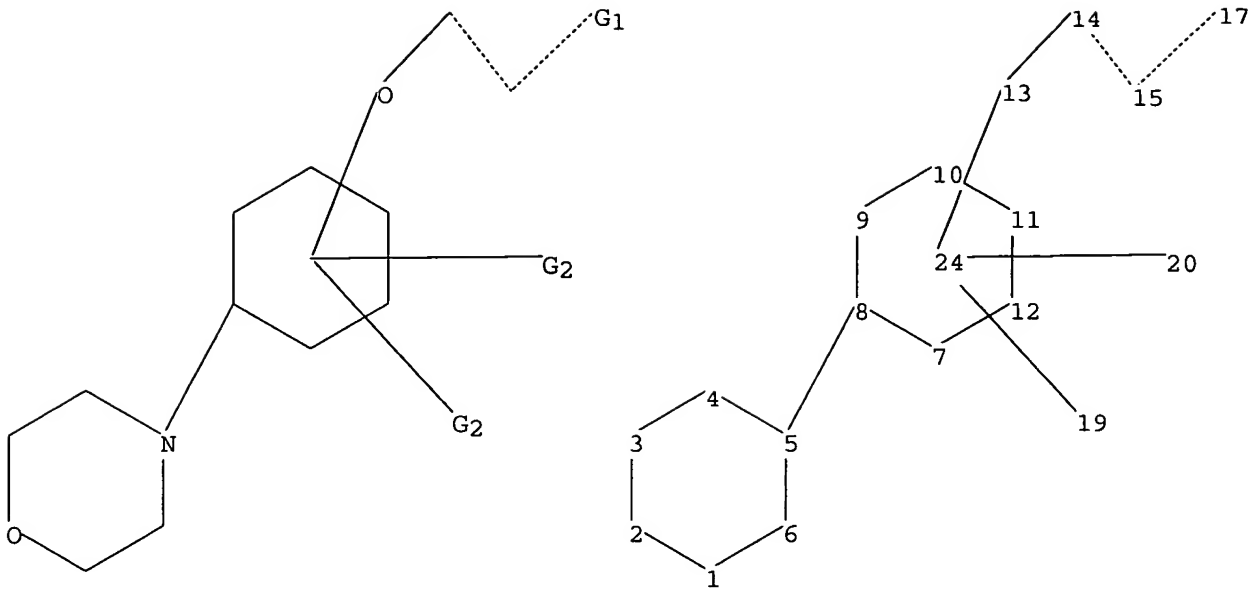
Structure attributes must be viewed using STN Express query preparation.

=> s l5 subset=l3 full
FULL SUBSET SEARCH INITIATED 06:22:31 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 520 TO ITERATE

100.0% PROCESSED 520 ITERATIONS 515 ANSWERS
SEARCH TIME: 00.00.01

L6 515 SEA SUB=L3 SSS FUL L5

=>
Uploading C:\Program Files\Stnexp\Queries\QUERIES\106746842.str



chain nodes :
13 14 15 17 19 20
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
5-8 13-14 14-15 15-17
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-8 13-14 14-15 15-17
exact bonds :
7-8 7-12 8-9 9-10 10-11 11-12
isolated ring systems :
containing 1 : 7 :

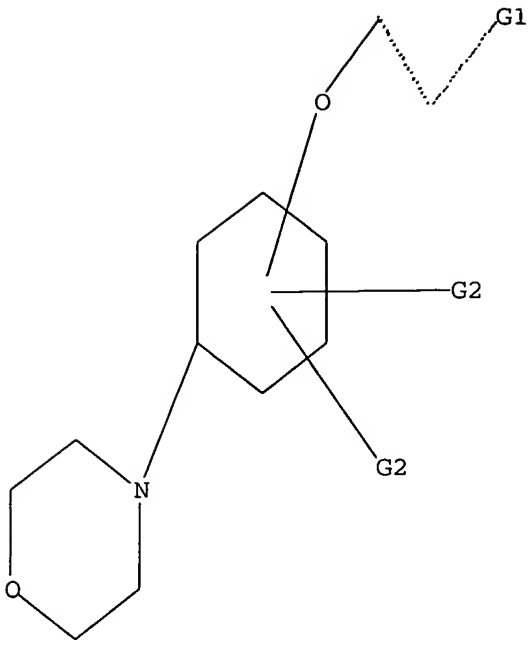
G1:C,O,S

G2:C,H,O

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

L7 STRUCTURE UPLOADED

=> d
L7 HAS NO ANSWERS
L7 STR



G1 C,O,S

G2 C,H,O

Structure attributes must be viewed using STN Express query preparation.

```
=> s l7 subset=l6 full
FULL SUBSET SEARCH INITIATED 06:24:13 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -     31 TO ITERATE

100.0% PROCESSED      31 ITERATIONS                              22 ANSWERS
SEARCH TIME: 00.00.01

L8            22 SEA SUB=L6 SSS FUL L7

=> s l8 and caplus/lc
      45042485 CAPLUS/LC
L9           21 L8 AND CAPLUS/LC

=> s l8 not l9
L10           1 L8 NOT L9

=> d

L10  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   807313-63-9  REGISTRY
CN   Morpholine, 4-[(1R,2R)-2-[4-(3,4-dimethoxyphenyl)butoxy]cyclohexyl]-, rel-
     (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C22 H35 N O4
CI   COM
SR   CA
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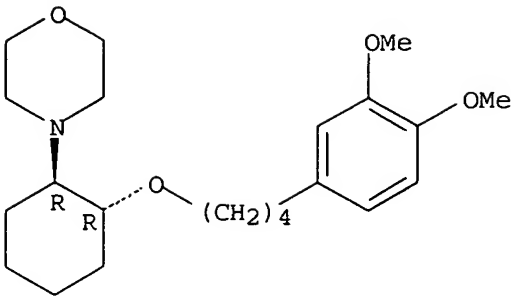
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

=> d ed l10

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
ED Entered STN: 03 Jan 2005

=> fil caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 252.89 253.10

FILE 'CAPLUS' ENTERED AT 06:24:57 ON 18 MAR 2005
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FILE COVERS 1907 - 18 Mar 2005 VOL 142 ISS 12
FILE LAST UPDATED: 16 Mar 2005 (20050316/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l9
L11 6 L9

=> d ibib abs hitstr l11 1-6

L11 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:996122 CAPLUS
DOCUMENT NUMBER: 141:424107
TITLE: Preparation of 1-[2-(2-phenylethoxy)cyclohexyl]pyrroli dinol derivatives for treatment of arrhythmia
INVENTOR(S): Beatch, Gregory N.; Choi, Lewis Siu Leung; Jung, Grace; Liu, Yuzhong; Plouvier, Bertrand; Wall,

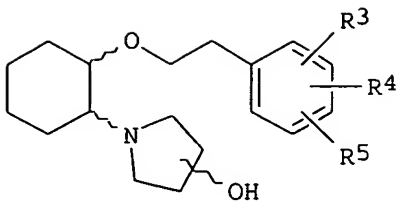
Richard; Zhu, Jeff; Zolotoy, Alexander; Barrett, Anthony G. M.
PATENT ASSIGNEE(S): Cardiome Pharma Corp., Can.
SOURCE: PCT Int. Appl., 381 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004099137	A1	20041118	WO 2003-US34655	20031031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005038256	A1	20050217	US 2004-862157	20040604
WO 2005016242	A2	20050224	WO 2004-US18050	20040604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

US 2003-467159P	P	20030502
US 2003-476083P	P	20030604
US 2003-475884P	P	20030605
US 2003-475912P	P	20030605
US 2003-476447P	P	20030605
US 2003-489659P	P	20030723
US 2003-493392P	P	20030807
US 2003-516486P	P	20031031

OTHER SOURCE(S): MARPAT 141:424107
GI



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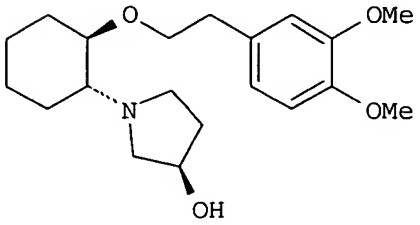


II

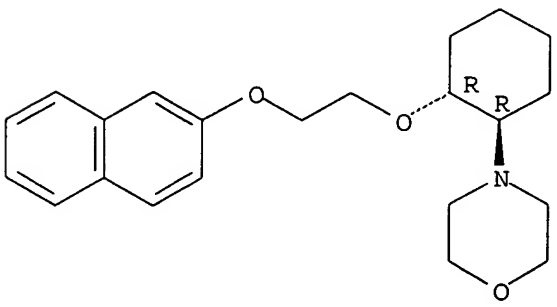
AB Title compds. I [wherein R3-R5 = independently H, OH, alkoxy; with the proviso that R3-R5 cannot all be H; or pharmaceutically acceptable salts, esters, amides, complexes, chelates, stereoisomers, stereoisomeric mixts., geometric isomers, crystalline or amorphous forms, metabolites, metabolic precursors, and prodrugs thereof] were prepared for the treatment of arrhythmia. Compds. of the invention may be also incorporated in compns. and kits. For example, (1R,2R)/(1S,2S)-1-[(3R)-benzyloxypyrrolidinyl]cyclohexan-2-ol (preparation given) was converted to the mesylate and then treated with the alkoxide produced by reaction of 3,4-dimethoxyphenethyl alc. with NaH to afford the ether (70%). Resolution of the diastereomeric mixture, followed by deprotection using Pd/C in 37% HCl provided II•HCl. X-ray structure determination confirmed the absolute configuration and structural assignment. In cardiovascular assays in rats, the II•HCl reduced the arrhythmia score in treated animals to 50% of that shown by control animals at an infusion rate of 1.4 μmol/kg/min and demonstrated low CNS toxicity with a therapeutic index of 18.1.

IT **244762-67-2P**, (1R*,2R*)-2-(4-Morpholinyl)-1-[2-(2-naphthoxy)ethoxy]cyclohexane **244762-69-4P 244762-82-1P 795282-14-3P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiarrhythmic; preparation of [(phenylethoxy)cyclohexyl]pyrrolidinol derivs. for treatment of arrhythmia)

RN 244762-67-2 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-69-4 CAPLUS
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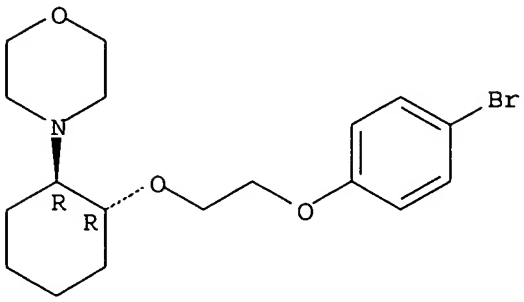
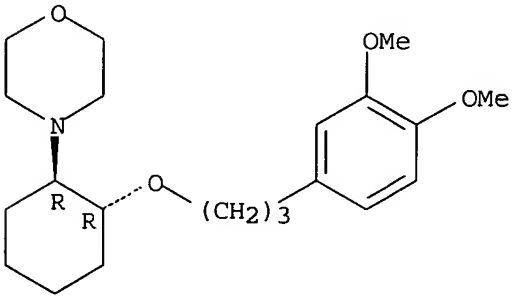
Relative stereochemistry.



RN 244762-82-1 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

RN 795282-14-3 CAPLUS
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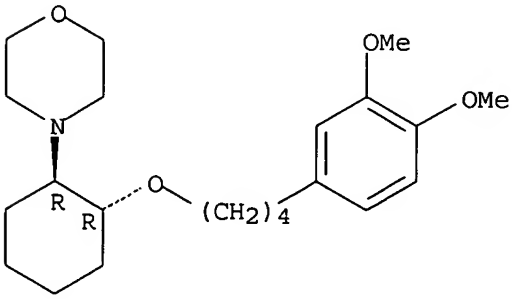
Relative stereochemistry.



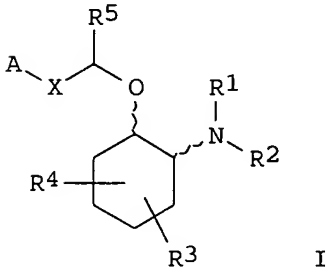
● HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:396011 CAPLUS
DOCUMENT NUMBER: 141:190792
TITLE: Preparation of aminocyclohexyl ethers as ion channel modulating compounds
INVENTOR(S): Bain, Allen I.; Longley, Cindy J.; Beatch, Gregory N.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Plouvier, Bertrand M. C.; Zhu, Jiqun; Zolotoy, Alexander B.; Yong, Sandro L.
PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.
SOURCE: Can. Pat. Appl., 158 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2268590	AA	20001012	CA 2000-2268590	19990412

PRIORITY APPLN. INFO.: CA 2000-2268590 19990412
OTHER SOURCE(S): MARPAT 141:190792
GI



I

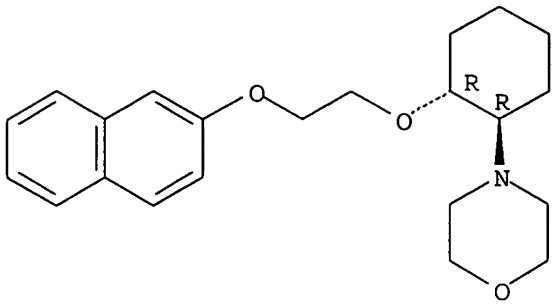
AB The title amines [I; R1, R2 = H, alkyl, alkoxyalkyl, etc.; NR1R2 = ring such as morpholino, 3-azabicyclo[3.2.2]nonane, etc.; R3, R4 = H, OH, alkyl, alkoxy; or when R3 and R4 are attached to the same ring atom, may together form a spiro 5-6 membered heterocyclic ring; X = a bond, alkenylene, etc.; A = hydrophobic moiety such as Ph, naphthyl, indenyl, etc.; R5 = H, alkyl, aryl, CH2Ph], useful as ion channel modulating compds. were prepared E.g., a multi-step synthesis of (±)-trans-[2-(4-morpholinyl)-1-(2-naphth-2-ylethoxy)]cyclohexane.HCl, starting from morpholine and cyclohexene oxide, was given. The compds. I were tested in various tests (biol. data given). The compds. I may be incorporated in compns. and kits. The present invention also discloses a variety of in vitro and in vivo uses for the compds. I and compns., including the treatment of arrhythmia and the production of analgesia and local anesthesia.

IT **244762-66-1P 244762-67-2P 244762-68-3P**
244762-69-4P 244762-82-1P 244763-07-3P
244763-08-4P 244763-09-5P 244763-10-8P
244763-23-3P 244763-24-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminocyclohexyl ethers as ion channel modulators)

RN 244762-66-1 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-,

hydrochloride, rel- (9CI) (CA INDEX NAME)

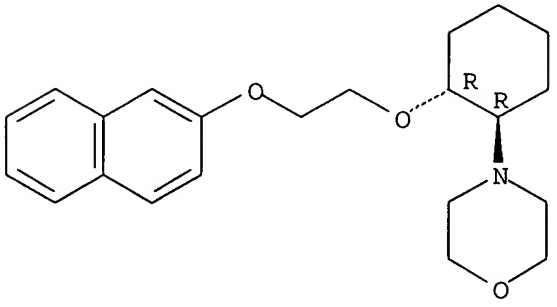
Relative stereochemistry.



● HCl

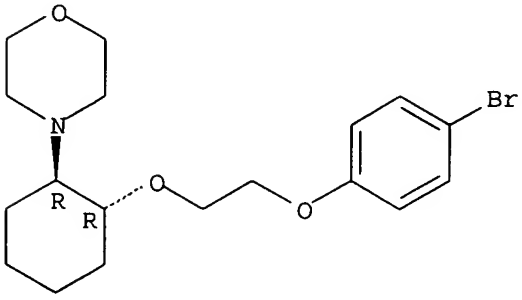
RN 244762-67-2 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-68-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

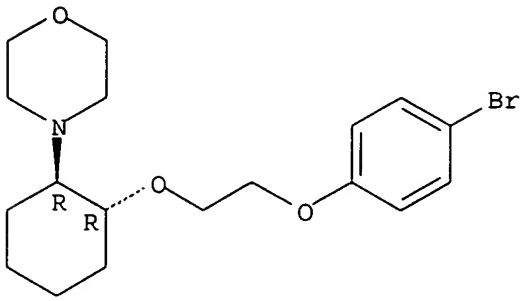


● HCl

RN 244762-69-4 CAPLUS

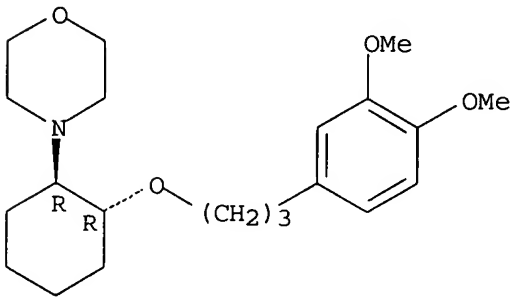
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-82-1 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

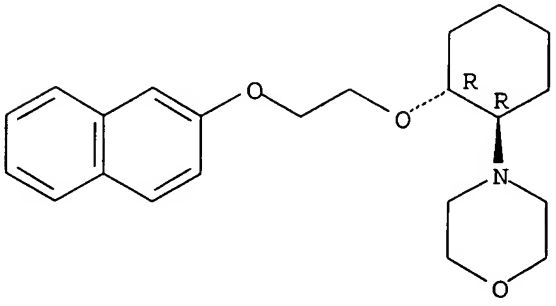
Relative stereochemistry.



● HCl

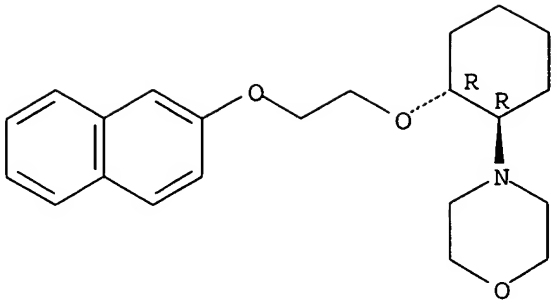
RN 244763-07-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



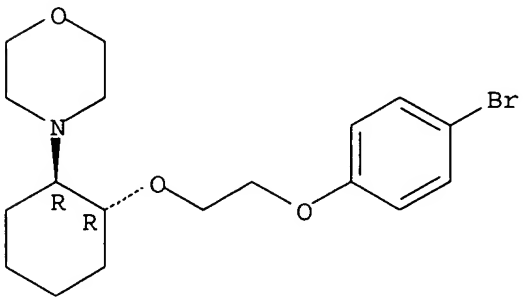
RN 244763-08-4 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



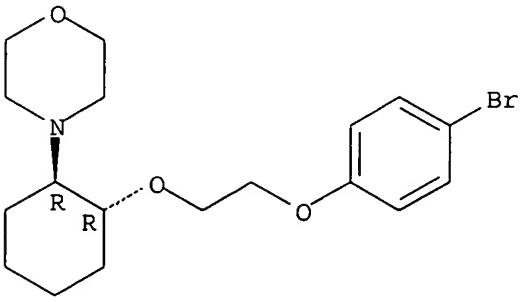
RN 244763-09-5 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



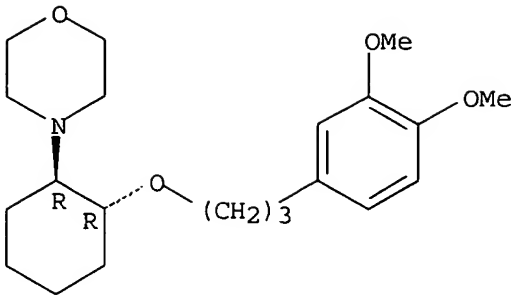
RN 244763-10-8 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



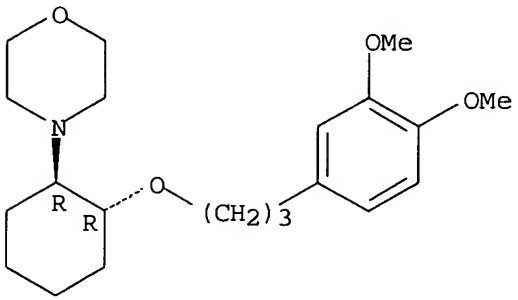
RN 244763-23-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



RN 244763-24-4 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



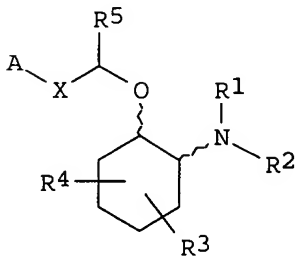
L11 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:640819 CAPLUS
DOCUMENT NUMBER: 131:257571
TITLE: Preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents
INVENTOR(S): Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.; Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun; Zolotoy, Alexander B.
PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950225	A1	19991007	WO 1999-CA280	19990401
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326777	AA	19991007	CA 1999-2326777	19990401
AU 9930215	A1	19991018	AU 1999-30215	19990401
AU 751772	B2	20020829		

TR 200002796	T2	20001221	TR 2000-200002796		19990401
EP 1087934	A1	20010404	EP 1999-911550		19990401
EP 1087934	B1	20040225			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI					
BR 9909282	A	20011016	BR 1999-9282		19990401
EE 200000583	A	20020215	EE 2000-583		19990401
JP 2002509908	T2	20020402	JP 2000-541135		19990401
NZ 507169	A	20040227	NZ 1999-507169		19990401
AT 260240	E	20040315	AT 1999-911550		19990401
EP 1422217	A2	20040526	EP 2004-2165		19990401
EP 1422217	A3	20040616			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, CY					
PT 1087934	T	20040730	PT 1999-911550		19990401
ES 2217742	T3	20041101	ES 1999-911550		19990401
ZA 2000005195	A	20020627	ZA 2000-5195		20000927
NO 2000004897	A	20001113	NO 2000-4897		20000929
US 2005020481	A1	20050127	US 2003-674684		20030929
PRIORITY APPLN. INFO.:			US 1998-80347P	P	19980401
			US 1999-118954P	P	19990205
			US 1999-283873	B2	19990331
			EP 1999-911550	A3	19990401
			WO 1999-CA280	W	19990401
			US 2000-680988	B1	20001006

OTHER SOURCE(S): MARPAT 131:257571

GI



I

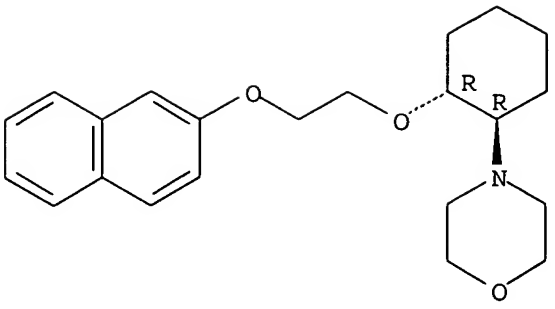
AB RZCHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, -naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepared as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compound trans-I.

IT **244762-66-1P 244762-67-2P 244762-68-3P**
244762-69-4P 244762-82-1P 244762-83-2P
244763-07-3P 244763-08-4P 244763-09-5P
244763-10-8P 244763-23-3P 244763-24-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RN 244762-66-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

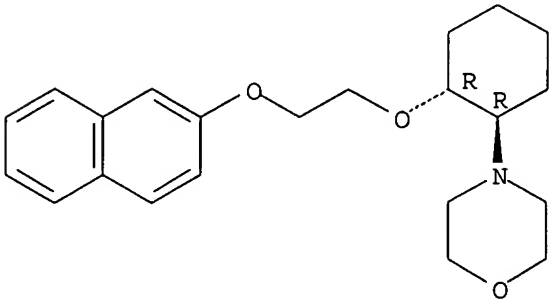
Relative stereochemistry.



● HCl

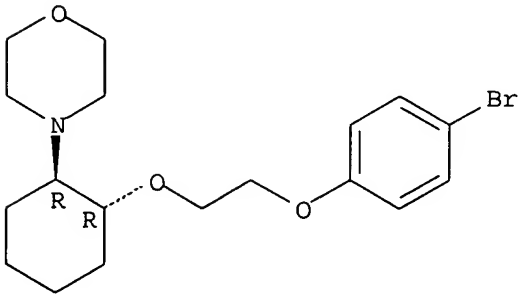
RN 244762-67-2 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-68-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

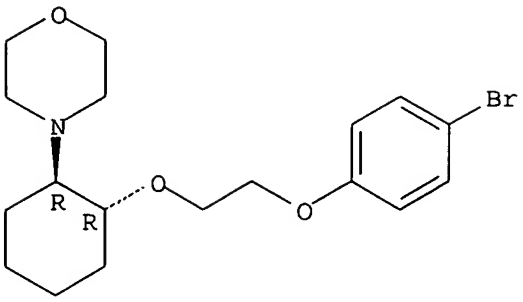
Relative stereochemistry.



● HCl

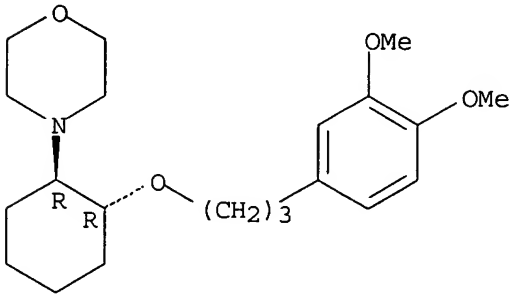
RN 244762-69-4 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-82-1 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

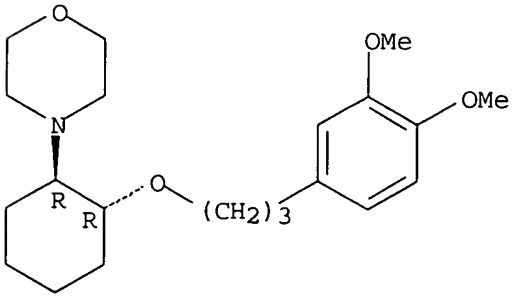
Relative stereochemistry.



● HCl

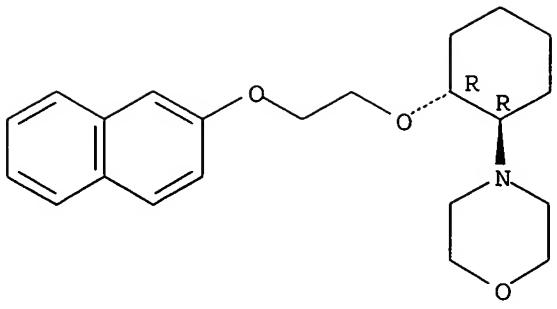
RN 244762-83-2 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



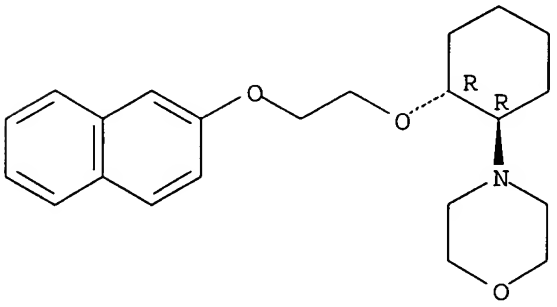
RN 244763-07-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



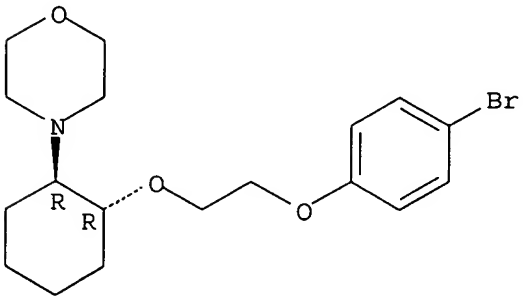
RN 244763-08-4 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



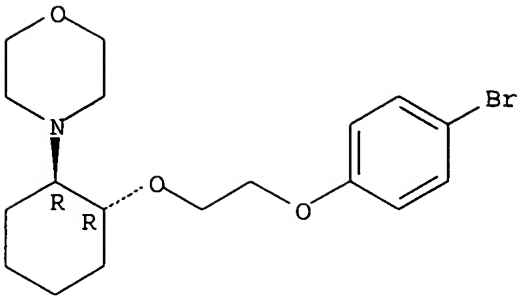
RN 244763-09-5 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



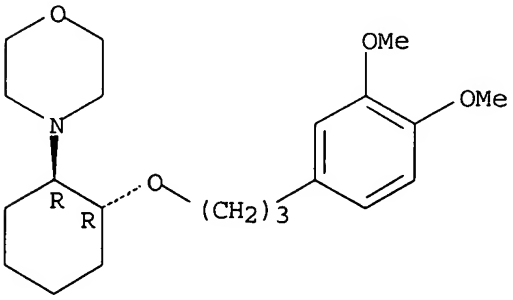
RN 244763-10-8 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



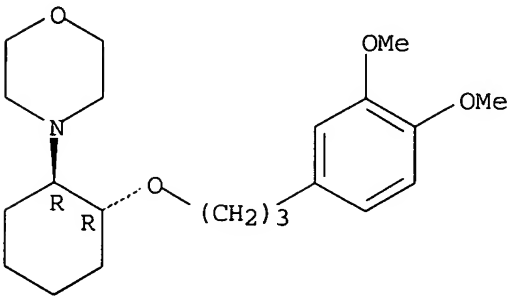
RN 244763-23-3 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

Rotation (+). Absolute stereochemistry unknown.



RN 244763-24-4 CAPLUS
CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

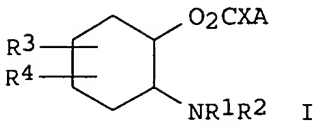
L11 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:400459 CAPLUS
DOCUMENT NUMBER: 127:108837
TITLE: Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.
INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.
PATENT ASSIGNEE(S): University of British Columbia, Can.
SOURCE: U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5637583	A	19970610	US 1994-313691	19940927
CA 2172513	AA	19950330	CA 1994-2172513	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
US 5885984	A	19990323	US 1997-807728	19970227
US 6174879	B1	20010116	US 1999-271087	19990317

PRIORITY APPLN. INFO.: US 1993-126575 B2 19930924
US 1994-313691 A3 19940927
US 1997-807728 A3 19970227

OTHER SOURCE(S): MARPAT 127:108837
GI



I

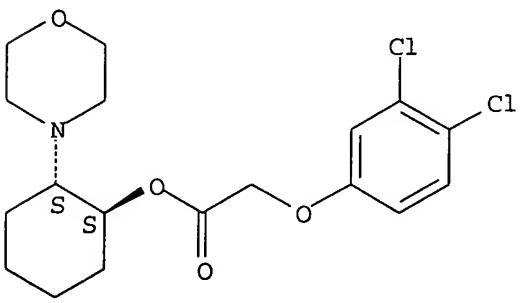
AB Title compds. [I; X = bond, (CH2)nY (n = 1, 2, 3; Y = bond, O, S), CH(R12)Y (R12 = alkyl, saturated carbocyclyl, Ph, PhCH2), C(R13):CH (R13 = H, alkyl, Ph); R1, R2 = H, alkyl, alkoxyalkyl, aralkyl; R1R2N = (substituted) (ring-fused) heterocyclyl; R3, R4 = H, OH, alkyl, alkoxy, points of attachment of a spiro 5- or 6-membered heterocyclic ring containing 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepared Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in CHCl3 to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8 μmoles/kg/min in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

IT **169191-23-5P 169191-37-1P 169191-52-0P**
192446-66-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

RN 169191-23-5 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

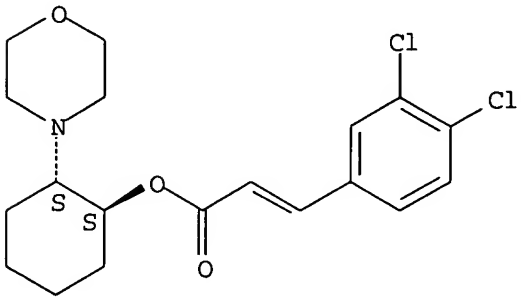
Relative stereochemistry.



● HCl

RN 169191-37-1 CAPLUS
CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

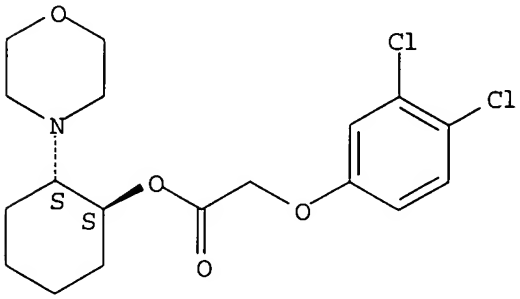
Relative stereochemistry.
Double bond geometry unknown.



● HCl

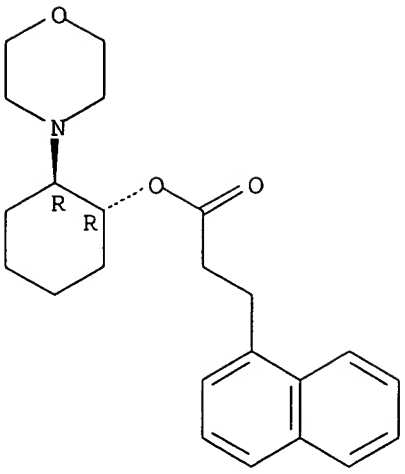
RN 169191-52-0 CAPLUS
CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 192446-66-5 CAPLUS
CN 1-Naphthalenepropanoic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

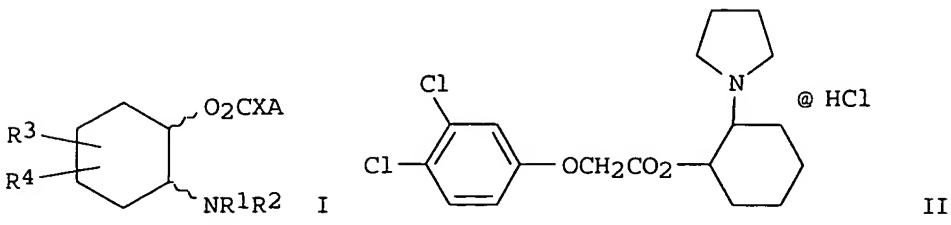
Relative stereochemistry.



L11 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:867587 CAPLUS
DOCUMENT NUMBER: 123:286082
TITLE: Preparation of heterocyclohexyl esters as antiarrhythmics
INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.
PATENT ASSIGNEE(S): University of British Columbia, Can.
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508544	A1	19950330	WO 1994-CA513	19940923
W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2172513	AA	19950330	CA 1994-2172513	19940923
AU 9476502	A1	19950410	AU 1994-76502	19940923
EP 720605	A1	19960710	EP 1994-926755	19940923
EP 720605	B1	20011219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211135	E	20020115	AT 1994-926755	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923

PRIORITY APPLN. INFO.: US 1993-126575 A 19930924
WO 1994-CA513 W 19940923
OTHER SOURCE(S): MARPAT 123:286082
GI



I II

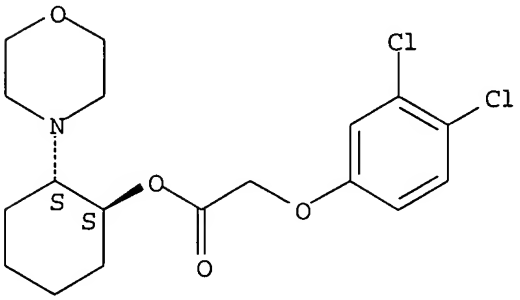
AB Title compds. I (X = bond, (CH2)nY, CH(R12)Y, CR13:CH wherein n = 1-3, Y = bond, O, S, R12 = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH2, R13 = H, C1-6 alkyl, Ph; R1, R2 =H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R1R2 = (substituted)heterocyclyl; R3, R4 = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepared I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohene oxide and water were reacted to give (±)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compound (±)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

IT **169191-23-5P 169191-37-1P 169191-39-3P**
169191-52-0P 169191-66-6P 169191-68-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclohexyl esters as antiarrhythmics)

RN 169191-23-5 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.

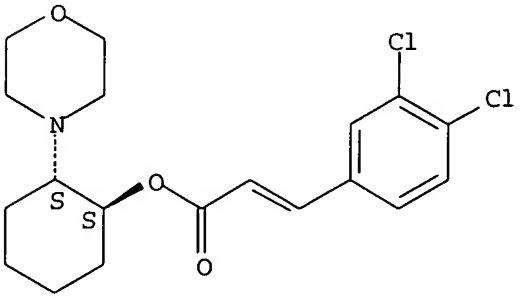


● HCl

RN 169191-37-1 CAPLUS

CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

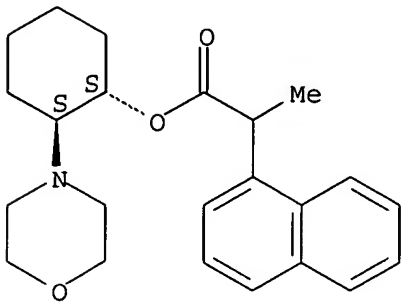
Relative stereochemistry.
Double bond geometry unknown.



● HCl

RN 169191-39-3 CAPLUS
CN 1-Naphthaleneacetic acid, α-methyl-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

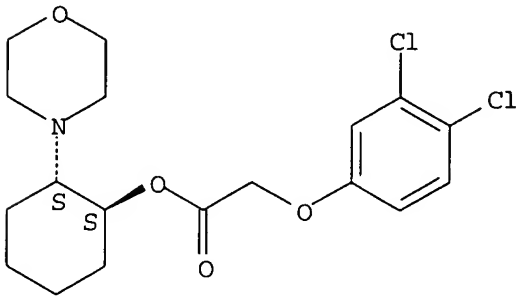
Relative stereochemistry.



● HCl

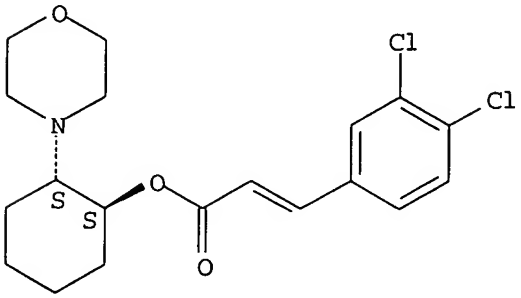
RN 169191-52-0 CAPLUS
CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



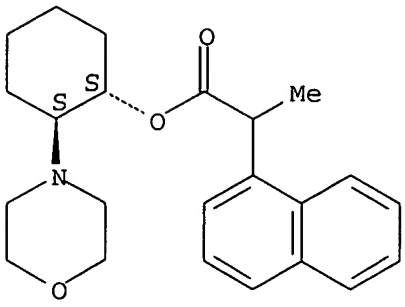
RN 169191-66-6 CAPLUS
CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



RN 169191-68-8 CAPLUS
CN 1-Naphthaleneacetic acid, α-methyl-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L11 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1959:39941 CAPLUS
DOCUMENT NUMBER: 53:39941
ORIGINAL REFERENCE NO.: 53:7177i,7178a-i,7179a-i,7180a-i,7181a
TITLE: Mechanism of chemical reactions. XVIII. Specific catalytic condensations with dihalides. 1. Conversion of aliphatic-aromatic dichlorides into amines with properties of local anesthetics
AUTHOR(S): Kindler, Karl; Hansen, Werner; Koebke, Jurgen
CORPORATE SOURCE: Univ. Hamburg, Germany
SOURCE: Ann. (1958), 617, 25-54
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 53:39941

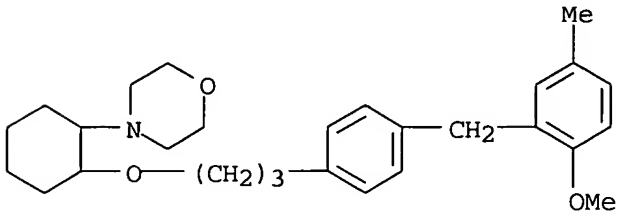
AB cf. C.A. 52, 9015g. PhCH2CH2OH (980 g.) at 130° was treated dropwise with 1 kg. SOCl3, heated another 1.5 hrs., giving 1.012 kg. PhCH2CH2Cl, b10 78-9°, 5 moles of which with 75 g. paraformaldehyde and 75 g. anhydrous ZnCl2, stirred 30 min. at 45°, treated 6.5 hrs. with a rapid stream of HCl (keeping a slight pressure for 30 min.), washed repeatedly with saturated aqueous NaCl, and then with aqueous NaCl and NaHCO3 to insure complete removal of HCl and ZnCl2, and fractionated gave 337 g. 4-ClCH2CH2C6H4CH2Cl (I), b9 137-8°, m. 34-5° (MeOH-PrOH with traces H2O). Similarly, 8.4 moles SOCl2 and 8 moles Ph(CH2)3OH gave 1.1 kg. Ph(CH2)3Cl, b8 86-88°, 775 g. of which with 75 g. paraformaldehyde gave 345 g. 4-Cl(CH2)3C6H4CH2Cl (II), b9 150-2°, n20D 1.5468. I with excess morpholine (III) in xylene, heated 14 hrs. at 125° gave p-(RCH2CH2)C6H4CH2R (R = morpholino), b0.8 184-6°; dipicrate, m. 190-2°. Similarly III and II gave p-RCH2CH2CH2C6H4CH2R, b0.9 196-8°; dipicrate, m. 202-3°. These derivs. of III were used in judging the purity of various prepns. of I and II. Mesitylene (IV) and other aromatic hydrocarbons and ethers (in excess) were condensed with I or II by using min. amts. of FeCl2 as catalyst, and passing CO2-free air through the mixture to remove HCl. Excessive amts. of FeCl3 gave greatly decreased yields. The following monochlorides, p-R'CH2C6H4CH2CH2Cl (V) were obtained from 0.1 mole I (other reactant, mg. FeCl3, temperature, reaction time in min. R', b.p./mm., and % yield of V given): C6H6, 90, 90°, 80, Ph, 185-7°/8, 59; IV, 0.06, 115°, 45, 2,4,6-MeC6H2, 207-9°/8, 78; MeOPh, 60, 110°, 60, 4-(MeO)C6H4, 212-15°/10, 84; 2-MeC6H4OMe, 15, 115°, 15, 3,4-Me(MeO)C6H3, 229-33°/16, 76; 2-ClC6H4OMe, 30, 115°, 35, 3,4-Cl(MeO)C6H3, 215-17°/0.7, 58. Similarly formed from II were the following p-R'CH2C6H4CH2CH2CH2Cl (VI) (with similar data given): naphthalene, 67, 100°, 25, α-C10H7, 221-23°/1.5, 59; 1-methylnaphthalene, 81, 100°, 20, 4-MeC10H6, 232-4°/1.1, 68; Tetralin, 50, 120°, 100,

5,6,7,8-tetrahydro-β-naphthyl, 214-16°/1.4, 58; IV, 0.17,
115°, 25, 2,4,6-Me3C6H2, 196-99°/1.3, 79; PhMe, 30,
100°, 30, 4-MeC6H4, 205-8°/10, 60; PhEt, 30, 110°,
40, 4-EtC6H4, 214-17°/10, 73; PhPr, 15, 115°, 60, 4-PrC6H4,
180-1°/0.8, 66; 1,4-Me2C6H4, 30, 110°, 20, 2,5-Me2C6H3,
214-18°/10, 70; 1,2-Me2C6H4, 90, 110°, 90, 3,4-Me2C6H3,
220-23°/10, 73; 4-iso-PrC6H4, 45, 155-60°, 70,
2,5-Me(iso-Pr)C6H3, 186-90°/0.8, 70; PhCl, 15, 115°, 35,
4-ClC6H4, 174-77°/0.8, 22; p-ClC6H4OH, 4, 100°, 85,
5,2-Cl(HO)C6H3, 226-30°/1.2, 57; o-ClC6H4OH, 5,
100°, 3,4-Cl(HO)C6H3, 90, 232-36°/1.1, 63; MeOPh, 11,
100° 35, 4MeOC6H4, 185°/1.5, 68; EtOPh, 24, 100°, 30,
4-EtOC6H4, 208-10°/2.4, 65; PrOPh, 25, 100°, 65, 4-PrOC6H4,
214-18°/2.2, 69; BuOPh, 10, 100°, 25, 4-BuOC6H4,
207-10°/1.2, 59; 2-ClC6H4OMe, 6, 100°, 20, 3,4-Cl-
(MeO)C6H3, 213°/1.3, 73; 2-ClC6H4OEt, 7, 100°, 40, 3,4-
Cl(EtO)C6H3, 225-27°/2, 66; 2-ClC6H4OPr, 18, 130°, 25,
3,4-Cl(PrO)C6H3, 219-21°/0.8, 66; 2-iso-PrC6H4Cl, 17, 130°,
30, 3,4-Cl(iso-Pr)C6H3, 204-6°/0.9, 52; 2-ClC6H4Bu 18, 125°,
15, 3,4-Cl(Bu)C6H3, 238-40°/1.3, 64; 2-Me-C6H4OMe, 6, 100°,
120, 3,4-Me(MeO)C6H3, 200-3°/1.5, 72; 4-MeC6H4OMe (VII), 23,
110°, 130, 5,2-Me(MeO) C6H3 (VIIa), 204-6°/2.6, 62;
2-MeC6H4OEt, 15, 100°, 30, 3,4-Me(EtO)C6H3, 201-3°/0.9, 75;
2-MeC6H4OPr, 16, 125°, 30, 3,4-Me(PrO)C6H3, 207-9°/1.3, 66;
2-MeC6 H4OBu, 28, 145°, 65, 3,4-Me(BuO)C6H3, 217-19°/1.6,
63; 2-MeC6H4OCH2CH2OEt, 66, 120°, 170, 3,4-Me(EtOCH2 CH2)C6H3,
225-32°/1.5, 78; Ph2O, 12, 105°, 140, 4-PhOC6H4,
225-7°/0.7, 65; 1,2(MeO)2C6H4, 25, 120°, 25, 3,4-
(MeO)2C6H3, 212-14°/1, 62; 1,3-(MeO)2C6H4, 11, 110°, 215,
2,4-(MeO)2C6H3, 235-7°/4, 74; 1,2,3(MeO)2C6H3, 18, 130°, 15,
2,3,4-(MeO)3C6H2, 229-31°/1.5, 69; 1-MeO-C10 H7, 9, 100°,
20, 4-MeOC10H6, 243-6°/1.3, 68; dihydrosaf-role 30, 100°,
50, 3,4-(CH2O2)-6-PrC6H2, 214-19°/0.8, 62; dihydroeugenol Me ether,
30, 110°, 65, 3,4,6(MeO)2PrC6H2, 205-8°/0.4, 69;
dihydroanethole, 30, 110°, 35, 2,5-(MeO) PrC6H3, 191-4°/0.6,
61. In forming the following VI, from 0.15-0.2 mole II, anhydrous AlCl3 or
ZnCl2 was used (reactant, mg. of catalyst, temperature and reaction period in
min, R', b.p./ mm. and yield given): C6H6, 105 AlCl3, 90°, 120, Ph,
191- 2°/6, 42; PhF, 193 AlCl3, 90°, 200, 4-FC6H4,
180-3°/3, 25; PHCl, 147 AlCl3, 105°, 60, 4-ClC6H4,
203-4°/2.7, 20; PhBr, 118 AlCl3, 110°, 60, 4-BrC6H4,
218-20°/3.5, 17; VII, 42 AlCl3, 110°, 90, VIIa,
198-200°/2.6, 83; Ph2O 9 AlCl3, 105°, 80, 4-PhOC6H4,
247-9°/2, 63; MeOPh, 12 ZnCl2, 100°, 70, 4-MeOC6H4,
209-11°/2.6, 70; VII, 32 ZnCl2, 110°, 35, VIIa,
198-200°/2.6, 74. V and VI were purified by repeated distns.; no
analyses are given. V and VI were condensed with primary or secondary
amines in Et3N or xylene, usually by heating 16-20 hrs. at 125°,
using sealed tubes when required. After removal of the solvent and excess
amine, the products were frequently extracted with Et2O converted into the HCl
salts, which after washing with Et2O were reconverted into the free bases
and extracted with Et2O. The exts. were washed with H2O and recoveries were
obtained both from the Et2O exts. and H2O-washings. From V the products
were p-RCH2C6H4CH2CH2R'' (VIII) (R'' = substituted amino group). V(R =
Ph) with MeNH2 in Et3N gave 79% VIII (R = Ph, R'' = NHMe), b1 149-51; HCl
salt, m. 191-2°: picrate, m. 95-6°. Similarly formed from
the appropriate V and III in xylene were 92% VIII (R = 4-MeOC6H4, R'' =
morpholino), b1 218-20°, and 89% VIII (R = 2,4,6-Me3C6H2; R' =
morpholino), b14 220-2°, n20D 1.5634. Similarly from the
appropriate V and amine were formed 63% VIII (R = 3,4-Me(MeO)C6H3, R'' =
Et2N), b0.3 175-8°, n20D 1.5458, and 76% VIII (R = 3,4-Cl(MeO)C6H3,
R'' = morpholino), b2 242-6°. Analogous condensation, usually
under similar conditions, were effected with the appropriate VI and
various amines giving the following compds. p-R'Ch2C6H4CH2CH2R'' (IX) (R',

R'', b.p./mm. % yield and n20D given): α-C10H7, morpholino, 252-4°/1.8, 89, -; 4-MeC10H6, morpholino, 260-2°/0.8, 92, -; 5,6,7,8-tetrahydro-β-naphthyl, morpholino, 243-6°/1.6, 94; -; tetrahydro-β-naphthyl, Et2N, 208-11°/0.6, 77, 1.5569; 2,4,6-Me3C6H2, morpholino, 233-5°/1.7, 92, -; 4-MeC6H4, morpholino, 193-5°/0.4, 82, 1.5582; 4-MeC6H4, Et2N, 173-5°/0.6, 73, 1.5401; 4-EtC6H4, morpholino, 203-6°/0.5, 83, 1.5548; 4-EtC6H4, Et2N, 175-8°/0.5, 72, 1.5381; 4-PrC6H4, Et2N, 194-7°/0.9, 65, 1.5338; 4-PrC6H4, morpholino, 216-19°/0.9, 72, 1.5504; 2,5-Me2C6H3, morpholino, 208-11°/0.5, 88, 1.5581; 2,5-Me2C6H3, Et2N, 174-77°/0.5, 71, 1.5407; 3,4-Me2C6H3, morpholino, 204-7°/0.4, 84, 1.5589; 3,4-Me2C6H3, Et2N, 181-4°/0.6, 67, 1.5417; 2,5-Me(iso-Pr)C6H3, morpholino, 243-5°/1.7, 83, -; 4-ClC6H4, Et2N, 190-2°/0.6, 1.5493; 5,2-Cl(HO)C6H3, morpholino, 270-1°/2.5 (with subsequent crystallization), 85, -; 3,4-Cl(HO)C6H3, morpholino, 260-4°/0.7 (with crystallization), 81 -; 4-MeOC6H4, morpholino, 239-40°/3, 92, -; 4-MeOC6H4, N-cyclohexyl methylamino, 242-4°/2, 78, -; 4-MeOC6H4, (CH2:CHCH2)2N, 232°/0.5, 78, -; 4-MeOC6H4, Pr2N, 213-15°/1.3, 60, -; 4-MeOC6H4, pyrrolidino, 206-8°/1, 93°, -; 4-EtOC6H4, morpholino, 232-4°/1.2, 89, -; 4-PrOC6H4, morpholino, 235-7°/1, 87, -; 4-BuOC6H4, morpholino, 254-6°/1.7, 88, -; 3,4-Cl(MeO)C6H3, morpholino, 242°/1.2, 86, -; 3,4-Cl(MeO)C6H3, MeNBu, 226-8°/1, 50, -; 3,4-Cl(EtO)C6H3, morpholino, 3,4-Cl(PrO)C6H3, morpholino, 250-2°/1.1, 87, -; 3,4-Cl(iso-PrO)C6H3, morpholino, 249-51°/1.4, 54, -; 3,4-Cl(BuO)C6H3, morpholino, 246-8°/1, 87, -; 3,4-Me(MeO)C6H3, morpholino, 226-8°/1, 89, -; in the following VIII. R = 3,4-Me(MeO)C6H4, and only R'', b.p./mm. and % yields are given: Et2N, 208°/0.4, 68, EtBuN, 206-9°/0.5, 76; Bu2N, 244-7°/0.7, 57; (CH2:CHCH2)2N, 230-2°/0.6, 80; 2-methyl-1-piperidyl, 229-32°/1, 83; 2,5-dimethyl-1-piperazinyl, 239-42°/1, 41. In the following VIII, R and R'' b.p/mm. and yields are given: 5,2-Me(MeO)C6H3, morpholino, 234-7°/1.1, 85; 3,4-Me(EtO), C6H3, morpholino, 221-23°/0.7, 91; 3,4-Me(EtO)C6H3, Et2N, 193-7°/0.6, 84, n20D 1.5362; 3,4-Me(PrO)C6H3, morpholino, 247-9°/1.3, 86; 3,4-Me(PrO)C6H3 Et2N, 195-8°, 67, n20D 1.5323; 3,4-Me(BuO)C6H3, morpholino, 244-6°/1.5, 93; 3,4-Me(EtOCH2CH2)C6H3, morpholino, 253-7°/1.2, 75; 4-PhOC6H4, morpholino, 263-5°/1.1, 87; 3,4-(MeO)2C6H3, morpholino, 232-4°/0.6, 88; 2,4-(MeO)2C6H3, morpholino, 232-3°/0.8, 89; 2,3,4-(MeO)3C6H2, morpholino, 246-7°/1.5, 87; 4-MeOC10H6, morpholino, 268-70°/0.8, 85; 3,4-(CH2O2)6-PrC6H2, morpholino, 242-4°/0.6, 61, n20D 1.5601; 3,4-(CH2O2)6-PrC6H2, Et2N, 206-9°/0.5, 62, n20D 1.5451; 3,4,6-(MeO)2PrC6H2, morpholino, 245-7°/0.7, 86, n20D 1.5538; 3,4,6-(MeO)2PrC6H2, Et2N, 209-12°/0.6, 78, n20D 1.5382; 2,5-(MeO)PrC6H3, morpholino, 230-2°/0.6, 87, n20D 1.5510; 2,5-(MeO)PrC6H3, Et2N, 190-2°/0.4, 71, n20D 1.5357; 3,4-Me(MeO)C6H3, MeOCH2CH2CH2NH, 219-22°/0.7, 84, n20D 1.5450. Na (0.1 g. atom) powdered by heating in 40 cc. boiling xylene was treated with a suitable amino alc. (usually β-morpholinoethanol (IX) in 10 cc. xylene, and heated 15 hrs. at 150° with the appropriate VI. The mixture was treated with Et2O and the organic phase washed with H2O, shaken with 6% HCl, and the resulting salt reconverted into the free ether with KOH, extracted with Et2O, washed and distilled to give the following p-derivs. of γ-phenylpropyl β-morpholinoethyl ether (p-substituent, b.p./mm., and % yield given): α-naphthylmethyl, 272°/1, 72; 4-FC6H4CH2, 236-9°/1.8, 81; 4-MeOC6H4CH2, 242-4°/0.8, 82; 3,4-Cl(PrO)C6H3CH2, 284-6°/2, 79; 3,4-Cl(BuO)C6H3CH2, 276-82°/1.0-1.3, 77; 3,4-Me(MeO)C6H3CH2, 258-60°/1.5, 85; 3,4-Me(EtO)C6H3CH2, 253-6°/0.9, 70; 3,4-Me(PrO)C6H3CH2, 262-4°/1.5, 67; 3,4-Me(EtOCH2CH2)C6H3CH2, 274-7°/1.5, 61; PhOC6H4CH2, 297-99°/0.7, 72; 2,4-(MeO)2C6H3CH2, 262-4°/1.0, 60. Formed analogously were the following [p-(4-methoxybenzyl)-γ-phenylpropyl]-

β-piperidinoethyl ether, 227-9°/0.7, 75; [p-(4-methoxy-3-methylbenzyl)-γ-phenylpropyl]-β-dibutylaminoethyl ether, 279-82°/1.1, 53; and [p-(2-methoxy-5-methylbenzyl)-γ-phenylpropyl]-2-morpholinocyclohexyl ether, 276-9°/1.3, 40. 2-O2NC6H4OMe (X) (0.6 mole) heated 90 min. at 115° with 0.2 mole 4-[Cl(CH2)3]C6H4CH2Cl and 90 mg. FeCl3 gave p-(4-methoxy-3-nitrobenzyl)-γ-phenylpropyl chloride (XI) which could not be distd; after removing excess X, 67 g. crude XI was treated with 52.3 g. III to give 49 g. crude, undistillable N-[(p-4-methoxy-3-nitrobenzyl)-γ-phenyl] morpholine, (XII), 18.5 g. of which, in 150 cc. MeOH was hydrogenated 8 hrs. with 10 g. moist Raney Ni at 2.5 atmospheric, filtered, treated with 6% HCl, and processed as above, to yield 53% 3-NH2 analog of XII, C21H28N2O2, b0.7 250-3°/1, m. 67-8°. p-[5,2-Me(MeO)C6H3CH2]C6H4(CH2)3Cl (XIII) (0.2 mole), heated and stirred 22 hrs. with 0.24 mole NaI in 200 cc. PrOH, evaporated, treated with H2O and the resulting crude iodide analog (XIIIa) of XIII was filtered; the aqueous solution was extracted repeatedly with Et2O, and these evaporated exts. were combined with XIIIa, b12 212-28° (total yield 78%). XIIIa (53.8 g.) with 18.2 g. KCN in 250 cc. 80% PrOH, stirred and refluxed 20 hrs., evaporated, dissolved in H2O and extracted with Et2O gave 33.2 g. crude p-(2-methoxy-5-methylbenzyl)-γ-phenylbutyronitrile (XIV), freed from residual XIIIa by heating with III in xylene and extracting with 6% HCl. Purified XIV, b1.5 202-9°. XIV (9.3 g.) hydrogenated and shaken with 20 g. moist Raney Ni in MeOH saturated with NH3, filtered, evaporated dissolved in dilute HCl, washed with Et2O, and made alkaline with KOH gave 5 g. p-(5,2-Me(MeO)C6H3CH2C6H4(CH2)4NH2, (XV), b0.8 194-7°. Formed analogously to XV with only slight modifications from the appropriate nitrile was p-(3,4-Me(MeO)C6H3CH2)C6H4(CH2)4NH2, very hygroscopic, b1 208-11°. A mixture of 14 g. p-(3,4-Me(MeO)C6H3CH2)C6H4(CH2)3CN, 13 g. III and 50 cc. MeOH was hydrogenated at 20° with Raney Ni as above to give 6.9 g. crude N-[p-(3-methyl-4-methoxybenzyl)-δ-phenylbutyl]morpholine (XVI), purified by treating in Et2O with BzCl and aqueous NaOH, separating the Et2O phase, treating with dilute HCl, and freeing the base with KOH to give 5.0 g. XVI, b1.5 242-5°; picrolonate, m. 210°. PhCH2Cl (0.1 mole) and 0.6 mole MeOPh (XVII) or 2-MeC6H4OMe and small amts. of FeCl3 reacted readily at 100° giving the usual type of condensation products (e.g. PhCH2C6H4Me) in yields of 80-87%; with large amts. of FeCl3 yields decreased, and in the absence of catalyst no condensations occured. Mesitylene reacted readily with 0.1 mole p-MeOC6H4CH2Cl and 0.012 mg. FeCl3. Ph(CH2)2Cl or Ph(CH2)3Cl, even in the presence of small amts. of FeCl3 failed to react with XVII. With large amts. of FeCl3, at 150°, HCl was liberated, but no identifiable products were isolated. In the presence of 0.0005 mole of certain inhibitors (notably substituted thiobenzamides and (Et2N)2CO), the yields of PhCH2C6H4OMe were decreased greatly, unless much larger amts. of FeCl3 were used. E.g. in the presence of 0.0005 mole N-thiobenzoylpiperidine (XVIII), the amount of FeCl3 had to be increased from the usual 1 mg. to 81 mg. to give a satisfactory yield of PhCH2C6H4OMe. Whereas 0.3 mole XVII, 0.1 mole PhCH2Cl, and 1 mg. FeCl3 at 115° gave 70% PhCH2C6H4OMe in 30 min., the introduction initially of 0.1 g. XVIII gave rise to neither HCl nor PhCH2C6H4OMe. Neither diethyl- nor phenylethylbarbituric acid served as inhibitors. PhCH2Cl (25.4 g.) and 60 mg. FeCl3 in PhNO2 reacted violently giving HCl and a resin, however, when 0.5 g. Me(CH2)4CONH2 or Me(CH2)16CONH2 was added to the original mixture no HCl was formed, even on heating several hrs., and PhCH2Cl was recovered almost quantitatively. Similar results were obtained when these amides were added to other arylmethyl chlorides, I, or II, even in the presence of such resin-forming catalysts as ZnCl2 or AlCl3. The statement is made that the above condensations (giving amines) can yield local anesthetics; no pharmacol. data are given.

IT **104397-47-9**, Morpholine, 4-[2-[3-[α-(6-methoxy-m-tolyl)-p-tolyl]propoxy]cyclohexyl]-
(preparation of)
RN 104397-47-9 CAPLUS
CN Morpholine, 4-[2-[3-[α-(6-methoxy-m-tolyl)-p-tolyl]propoxy]cyclohexyl]- (6CI) (CA INDEX NAME)



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.09	283.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.38	-4.38

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